



## Original investigation

# Maternal Smoking: A Life Course Blood Pressure Determinant?

Maria Cabral MPH<sup>1</sup>, Maria J. Fonseca PhD<sup>1</sup>,  
Camila González-Beiras BSc<sup>1</sup>, Ana C. Santos PhD<sup>1</sup>,  
Liane Correia-Costa PhD, MD<sup>1</sup>, Henrique Barros PhD, MD<sup>1</sup>

<sup>1</sup>EPIUnit, Institute of Public Health, University of Porto, Portugal

Corresponding author: Maria Cabral, MPH, EPIUnit, Institute of Public Health, University of Porto, Rua das Taipas, 135, 4050–600 Porto, Portugal. Telephone: +351 222 061 820; Email: [maria.cabral@ispup.up.pt](mailto:maria.cabral@ispup.up.pt)

## Abstract

**Introduction:** Exposure to maternal smoking early in life may affect blood pressure (BP) control mechanisms. We examined the association between maternal smoking (before conception, during pregnancy, and 4 years after delivery) and BP in preschool children.

**Methods:** We evaluated 4295 of Generation XXI children, recruited at birth in 2005–2006 and reevaluated at the age of 4. At birth, information was collected by face-to-face interview and additionally abstracted from clinical records. At 4-year follow-up, interviews were performed and children's BP measured. Linear regression models were fitted to estimate the association between maternal smoking and children's BP.

**Results:** Children of smoking mothers presented significantly higher BP levels. After adjustment for maternal education, gestational hypertensive disorders, and child's body mass index, children exposed during pregnancy to maternal smoking presented a higher systolic BP (SBP) z-score ( $\beta = 0.08$ , 95% confidence interval [CI] 0.04 to 0.14). In crude models, maternal smoking was associated with higher SBP z-score at every assessed period. However, after adjustment, an attenuation of the association estimates occurred ( $\beta = 0.08$ , 95% CI 0.03 to 0.13 before conception;  $\beta = 0.07$ , 95%CI 0.02 to 0.12;  $\beta = 0.04$ , 95%CI –0.02 to 0.10; and  $\beta = 0.06$ , 95%CI 0.00 to 0.13 for the first, second, and third pregnancy trimesters, respectively; and  $\beta = 0.07$ , 95%CI 0.02 to 0.12 for current maternal smoking). No significant association was observed for diastolic BP z-score levels.

**Conclusion:** Maternal smoking before, during, and after pregnancy was independently associated with systolic BP z-score in preschool children. This study provides additional evidence to the public health relevance of maternal smoking cessation programs if early cardiovascular health of children is envisaged.

**Implications:** Using observational longitudinal data from the birth cohort Generation XXI, this study showed that exposure to maternal smoking—before pregnancy, during pregnancy, and 4 years after delivery—was associated with a systolic BP-raising effect in children at the age of 4. The findings of this study add an important insight into the need to support maternal smoke-free environments in order to provide long-term cardiovascular benefit, starting as early as possible in life.

## Introduction

Smoking is worldwide the most common preventable cause of morbidity and mortality.<sup>1,2</sup> Every year, it is responsible for nearly 6 million deaths, of which more than 5 million result directly from smoking and over 600 000 occur in nonsmokers due to passive exposure.<sup>3</sup> Despite a global decrease in prevalence,<sup>4</sup> one billion adults are smokers.<sup>5</sup> Most are aged 20–40 years, the child-bearing age, and when more time is expected to be spent by parents with children.<sup>4</sup> This contributes to expose approximately 700 million children worldwide to second-hand smoke (SHS), mostly at home.<sup>6,7</sup> However, smoking influences the life course since intrauterine life. Research into maternal smoking during pregnancy suggests that alterations in fetal programming, in response to an adverse fetal environment, might be involved in the origins of chronic conditions later in life,<sup>8</sup> apart from increasing the risk of preterm birth, intrauterine growth restriction, and perinatal death. Later, during the pediatric period, it increases the risk of respiratory illnesses, neurobehavioral problems, and poor school performance.<sup>9</sup>

It has been hypothesized that SHS exposure contributes to atherosclerosis, as it promotes a permanent status of inflammation, leads to lipid accumulation in heart blood vessels and aorta,<sup>10</sup> and causes permanent vascular damage, and this process might begin in the fetal life.<sup>11</sup> Maternal smoking during pregnancy and SHS exposure during childhood may lead to long-lasting “programming” of blood pressure (BP) control mechanisms, increasing susceptibility to adverse outcomes, such as hypertension.<sup>12</sup>

Hypertension is the leading risk factor for severe cardiovascular outcomes.<sup>13</sup> In Portugal, where the leading cause of death is stroke, the risk of hypertension remains higher than in other developed countries,<sup>14</sup> and hypertension remains highly prevalent although increasing awareness and treatment resulted in decreased blood pressure levels.<sup>15</sup>

Growing evidence suggests that blood pressure tracks from childhood into adulthood,<sup>16</sup> reflecting a complex interaction of genetic, behavioral, environmental, and social determinants.<sup>17,18</sup> Evidence also suggests that primary hypertension is early detectable and occurs commonly in the young.<sup>19</sup> Additionally, the long-term health risks for children with hypertension can be substantial, which makes it essential to adopt measures to reduce these risks and optimize health outcomes. Still, it is unknown when BP becomes a valid predictor of long-term cardiovascular risk.

Instead of focusing on adult life, when disease is established, the possibility of assessing environmental exposures longitudinally from before conception through pregnancy and childhood provides a valuable asset to better understand diseases that have fetal or developmental origins.<sup>20</sup> Since there is a lack of report on the offspring's BP measured as early as at age 4, and there are inconsistent results relating children's exposure to maternal smoking and children blood pressure,<sup>13,21–26</sup> the present study quantified that association at specific periods—before pregnancy, during pregnancy, and 4 years after delivery using data from the Portuguese birth cohort, Generation XXI.

## Methods

### Subjects

Generation XXI assembled a cohort of 8647 children born between April 2005 and August 2006 at all five public maternity units that served the six municipalities of the metropolitan area of Porto, Portugal.<sup>27</sup> Of the invited mothers, 91.4% accepted to participate. Trained interviewers using structured questionnaires collected data on demographic and socioeconomic characteristics, lifestyles,

obstetric history, and anthropometrics, within 72 hours of delivery, during the hospital stay, by face-to-face interview. Clinical records were also reviewed at birth.

Four years after delivery, from April 2009 until April 2011, all children and their mothers were invited to a follow-up evaluation. Of the 8647 children evaluated at birth, 7459 were reevaluated (86% participation proportion). For families that were not able to participate in a face-to-face evaluation, a telephone interview was offered ( $n = 1472$ ), but BP was not recorded. For the purpose of the analysis, we additionally excluded multiple births ( $n = 215$ ); children who did not perform BP measurements as part of their physical assessment ( $n = 1257$ ); who did not live with their biological mothers ( $n = 87$ ); with missing information on preconception ( $n = 65$ ), pregnancy ( $n = 17$ ), and current ( $n = 3$ ) maternal smoking; mothers who reported to be smokers before and during pregnancy and never smokers when questioned at follow-up ( $n = 14$ ), missing information on mothers' educational level ( $n = 32$ ), and children's anthropometric measurements ( $n = 2$ ). Thus, the present analysis was based on the information of 4295 children. Participants were compared to those not included, and no differences were observed regarding mode of delivery, children's sex, or body mass index (BMI) and maternal smoking at follow-up. However, mothers of included children had a higher number of schooling years, 10.8 (4.2) vs. 10.0 (4.2),  $p < .001$ , and a lower proportion of tobacco smoking before (23.5% vs. 29.3%,  $p < .001$ ) and during pregnancy (21.1% vs. 25.7%,  $p < .001$ ).

### Assessment of Exposure and Covariates

Maternal socioeconomic characteristics, personal and family history of disease, obstetric history, and behavioral factors were self-reported. Maternal education corresponded to the number of completed schooling years at delivery. Parity was recorded as the number of deliveries, including the index one. Prepregnancy weight was self-reported after delivery and recorded to the nearest 0.1 kg. Height was measured in centimeters, to the nearest tenth, using a portable stadiometer.

Hypertensive disorders in pregnancy included the presence of chronic hypertension, gestational hypertension, or preeclampsia/eclampsia. Personal history of hypertension was considered present when participants recalled a medical diagnosis of this condition before the current pregnancy, while gestational hypertension or preeclampsia/eclampsia were considered only when explicitly recorded on obstetrical records as a diagnosis during the current pregnancy. When gestational hypertension and preeclampsia/eclampsia were simultaneously recorded in the medical record, the diagnosis of preeclampsia/eclampsia was considered. Smoking before and during pregnancy was recorded at delivery and considered if mothers had ever smoked within the 3 months previous to pregnancy and during each trimester of pregnancy. At 4-year follow-up, maternal smoking was considered if current smokers. We then grouped maternal smoking into three mutually exclusive categories: (1) never smoked (responded “no” for all three periods), (2) smoked before and/or after pregnancy but not during pregnancy, and (3) smoked during pregnancy (responded “yes” to the question on smoking during pregnancy independent of having also responded “yes” to the question on smoking before and/or after pregnancy).

### Blood Pressure and Other Clinical Measurements

Data on pregnancy and delivery characteristics, birthweight, and length were abstracted from medical records. Gestational age was considered as registered in medical files based on the biometric

measurement of the ultrasound or, if not available, on the date of the last menstrual period. At 4 years of age, measurements were performed by trained examiners. Weight was measured in light clothing to the nearest 0.1 kg using a digital scale, and height was measured to the nearest centimeter with a wall stadiometer. BMI was calculated as weight in kg divided by height in squared meters. BMI, age-, and sex-specific standard deviation scores (BMI z-scores) were computed according to the World Health Organization.<sup>28</sup>

BP was evaluated with an aneroid sphygmomanometer (Erka® Vario DeskModel) with an adequately sized cuff, by a trained examiner, twice with a 5-min interval between measurements, with the subject in a seated position and the antecubital fossa supported at heart level, after at least a 5-min rest. When the difference between the two determinations was larger than 5 mm Hg for systolic BP (SBP) or diastolic BP (DBP), a third measurement was taken, and the mean of the 2 closest values was considered. No significant differences were found between the average BP of the group with two measurements and the average of the second and third measurement in the group with three measurements (SBP: 106.8 vs. 106.7,  $p = .934$ ; DBP: 73.5 vs. 74.0,  $p = .617$ , respectively). BP SD score values were calculated, following the recommendations of the American Academy of Pediatrics, and children were classified as having high BP levels if SBP or DBP were above the 90th percentile for age, gender, and height.<sup>19</sup>

### Statistical Analysis

Continuous variables were presented as mean (SD), and Student  $t$  test was used for 2-group comparisons. Proportions were compared using chi-square tests. The association between maternal smoking and children's BP was evaluated fitting linear regression models (crude and adjusted  $\beta$  regression coefficients ( $\beta$ ) and 95 % confidence intervals [95% CI]). Univariable models were fitted for maternal smoking course and each for specific period—3 months before pregnancy; during first, second, and third pregnancy trimesters, and current smoking. Based on previous literature, we tested potential confounders and verified that maternal educational level, gestational hypertensive disorders, and child's BMI were associated with both exposure and outcome. Therefore, each of maternal smoking periods was further adjusted for these confounders.

Statistical analyses were performed using the Statistical Package for the Social Sciences (IBM® SPSS® Statistics), version 23.0. Statistical significance was considered with an  $\alpha$  critical value of 0.05.

### Ethics

The study was approved by the Portuguese Data Protection Agency, and ethical approval was obtained from the University of Porto Medical School and Centro Hospitalar São João ethics committee and the local ethics committees of the hospitals involved. A signed informed consent was obtained from all parents or the legal representative of participating children.

### Results

Table 1 displays maternal and child characteristics according to children BP status. Children with higher BMI more frequently presented a high BP level. Patients with high BP (20%) were significantly more frequent among mothers who had lower educational levels, higher prepregnancy BMI, or who smoked before conception and during pregnancy (during the first and third trimester).

Table 2 presents the association between maternal smoking and SBP and DBP z-scores. Smoking during pregnancy was associated with higher children's SBP z-score at 4 years compared to children of never smoking mothers, even after adjustment for potential confounders ( $\beta = 0.08$ , 95% CI 0.03 to 0.14). Maternal smoking was associated with higher SBP z-score levels at every period in the crude models; however, after adjustment, an attenuation of the association estimates occurred ( $\beta = 0.08$ , 95% CI 0.03 to 0.13 before conception;  $\beta = 0.07$ , 95% CI 0.02 to 0.12;  $\beta = 0.04$ , 95% CI -0.02 to 0.10, and  $\beta = 0.06$ , 95% CI 0.00 to 0.13 for the first, second, and third pregnancy trimesters, respectively; and  $\beta = 0.07$ , 95% CI 0.02 to 0.12 for current maternal smoking). No such association was observed for DBP z-score levels.

### Discussion

This study showed that maternal smoking was independently associated with children's BP at 4 years of age. We studied three different maternal smoking exposure periods: during preconception, considering the 3 months before pregnancy; during pregnancy, considering the first, second, and third trimesters; and at the time of follow-up evaluation. In all three periods, maternal smoking was positively associated with SBP z-score. This finding is in accordance with Oken and colleagues who also reported that children of mothers smoking in pregnancy and even before pregnancy presented higher SBP levels at age 3.<sup>21</sup> Similarly, Blake et al. reported higher SBP in children exposed to prenatal smoking<sup>29</sup> as well as Simonetti et al. who observed the same effect when considering parental passive smoking and offspring SBP z-score at age 6.<sup>13</sup>

The adverse consequences of active and passive smoking on cardiovascular health have been well demonstrated in adults.<sup>30</sup> The risk of ischemic heart disease is 2.6 times (95% CI 2.4 to 2.7) higher for men and 3.0 times (95% CI 2.8 to 3.2) for smoking women.<sup>31</sup> However, SHS exposure has emerged as a significant risk factor for CVD among nonsmokers, with a dose-dependent relationship.<sup>32-34</sup> Evidence has shown that the risk of coronary heart disease among SHS-exposed nonsmoking adults is 1.25 times (95% CI 1.17 to 1.32) higher than unexposed adults.<sup>35</sup>

In children, SHS exposure has been associated with respiratory illnesses and infections resulting in extra visits to the emergency department and medical expenditures.<sup>36</sup> Altered endothelial function and arterial morphology was also shown to be associated with SHS, indicating that childhood SHS exposure doubles the risk of carotid plaque in early adulthood.<sup>4,37,38</sup> However, to our knowledge, only four studies addressed the role of maternal smoking on BP as early as at preschool age.<sup>13,21,22,39</sup>

In our study, the observed associations could reflect sociodemographic or genetic confounding rather than a causal relationship, and it was why we adjusted for potential confounders, namely, maternal education and gestational hypertensive disorders,<sup>13</sup> but the adjustment did not change the results. However, the strength of the associations was attenuated when we further considered child's BMI, a suspected effect mediator, indicating that the association between maternal smoking and child's BP is partly explained by BMI. It was previously described an association between maternal smoking and a higher child's BMI, which in turn can lead to a higher BP.<sup>21</sup> We expect that a similar mechanism operates in our population.

Over the last decades, a new paradigm emerged to understand health risks such as obesity and cardiovascular disease, owed to the finding that environmental factors early in life and even in utero

**Table 1.** Mother and child characteristics according to children blood pressure status<sup>a</sup>

	Blood pressure centile		<i>p</i>
	<90th	≥90th	
Mothers' characteristics	<i>N</i> = 3435 (80)	<i>N</i> = 860 (20)	
Age at child's birth, years	29.57 (5.39)	29.36 (5.57)	.314
Educational level, years, %			
0–6	721 (76.9)	216 (23.1)	<.001
7–9	753 (76.3)	234 (23.7)	
10–12	995 (81.6)	225 (18.4)	
>12	966 (83.9)	185 (16.1)	
Prepregnancy BMI, kg/m <sup>2</sup>	23.77 (4.20)	24.84 (4.63)	<.001
Prepregnancy history of hypertension, %			
No	3247 (80.0)	813 (20.2)	.830
Yes	64 (79.0)	17 (21.0)	
Gestational hypertensive disorders, %			
No	3257 (80.1)	811 (19.9)	.546
Yes	178 (78.4)	49 (21.6)	
Parity			
1	2017 (80.8)	479 (19.2)	.108
>1	1418 (78.8)	381 (21.2)	
Maternal smoking course			
Never smoked	2449 (80.7)	586 (19.3)	.102
Smoked before and/or after pregnancy (but not during pregnancy)	285 (80.3)	70 (19.7)	
Smoked during pregnancy	701 (77.5)	204 (22.5)	
Smoked 3 months before pregnancy, %			
No	2651 (80.7)	633 (19.3)	.027
Yes	784 (77.5)	227 (22.5)	
Smoked during pregnancy, %			
First trimester			
No	2743 (80.6)	659 (19.4)	.037
Yes	692 (77.5)	201 (22.5)	
Second trimester			
No	2979 (80.3)	731 (19.7)	.187
Yes	456 (77.9)	129 (22.1)	
Third trimester			
No	3014 (80.4)	733 (19.6)	.048
Yes	421 (76.8)	127 (23.2)	
Currently smoking, %			
No	2594 (80.5)	627 (19.5)	.114
Yes	841 (78.3)	233 (21.7)	
Children's characteristics at birth			
Gender, %			
Female	1691 (79.8)	427 (20.2)	.825
Male	1744 (80.1)	433 (19.9)	
Birth weight, g	3181.04 (490.86)	3199.08 (484.63)	.334
Birth length, cm	48.74 (2.33)	48.74 (2.17)	.976
Gestational age, wk	38.63 (1.71)	38.66 (1.66)	.582
Preterm (<37 gestational weeks), %			
No	3172 (79.2)	802 (20.2)	.281
Yes	261 (82.3)	56 (17.7)	
Low birth weight (<2500 g), %			
No	3175 (79.8)	806 (20.2)	.194
Yes	260 (82.8)	54 (17.2)	
Children's characteristics at 4 years old			
Height, cm	105.82 (4.90)	106.96 (5.36)	<.001
BMI z-score	0.49 (1.01)	1.20 (1.29)	<.001
Systolic BP z-score	0.21 (0.60)	1.27 (0.71)	<.001
Diastolic BP z-score	0.27 (0.57)	1.16 (0.77)	<.001

Abbreviation: BMI, body mass index; BP, blood pressure.

Statistical significance in bold is considered at  $p < .05$ .<sup>a</sup>Values are expressed as mean (SD) or percentages. For each variable, the total may not add to 4295 due to missing data.

**Table 2.** Effect of maternal smoking on offspring blood pressure levels at 4 years-old—univariable and multivariable analysis

	SBP z-score		DBP z-score	
	$\beta$	95%CI	$\beta$	95%CI
Maternal smoking course				
Crude				
Never smoked	Ref	–	Ref	–
Smoked before and/or after pregnancy (but not during pregnancy)	0.06	–0.02 to 0.14	–0.04	–0.12 to 0.03
Smoked during pregnancy	<b>0.13</b>	<b>0.08 to 0.18</b>	0.00	–0.05 to 0.05
Adjusted <sup>a</sup>				
Never smoked	Ref	–	Ref	–
Smoked before and/or after pregnancy (but not during pregnancy)	0.04	–0.04 to 0.12	–0.04	–0.12 to 0.03
Smoked during pregnancy	<b>0.08</b>	<b>0.03 to 0.14</b>	0.00	–0.05 to 0.05
Maternal smoking 3 months before pregnancy <sup>b</sup>				
Crude	<b>0.12</b>	<b>0.07 to 0.18</b>	0.04	–0.01 to 0.09
Adjusted <sup>a</sup>	<b>0.08</b>	<b>0.03 to 0.13</b>	0.02	–0.03 to 0.07
Maternal smoking during first pregnancy trimester <sup>b</sup>				
Crude	<b>0.12</b>	<b>0.06 to 0.17</b>	0.03	–0.03 to 0.08
Adjusted <sup>a</sup>	<b>0.07</b>	<b>0.02 to 0.12</b>	0.00	–0.05 to 0.06
Maternal smoking during second pregnancy trimester <sup>b</sup>				
Crude	<b>0.10</b>	<b>0.03 to 0.16</b>	0.02	–0.05 to 0.08
Adjusted <sup>a</sup>	0.04	–0.02 to 0.10	–0.01	–0.07 to 0.05
Maternal smoking during third pregnancy trimester <sup>b</sup>				
Crude	<b>0.12</b>	<b>0.06 to 0.18</b>	0.02	–0.04 to 0.09
Adjusted <sup>a</sup>	<b>0.06</b>	<b>0.00 to 0.13</b>	–0.01	–0.07 to 0.06
Current maternal smoking <sup>b</sup>				
Crude	<b>0.11</b>	<b>0.06 to 0.17</b>	–0.00	–0.05 to 0.05
Adjusted <sup>a</sup>	<b>0.07</b>	<b>0.02 to 0.12</b>	–0.03	–0.08 to 0.02

Abbreviations:  $\beta$ , parameter estimate; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; CI, confidence interval.

Statistical significance in bold is considered at  $p < .05$ .

<sup>a</sup>Adjusted for maternal educational level, gestational hypertensive disorders and child's BMI.

<sup>b</sup>Reference category are nonsmoking mothers at each period.

can profoundly influence lifelong health.<sup>40,41</sup> We previously reported that the prevalence of unfavorable lifestyles and adiposity was high among these mothers, with the occurrence of risk factors highlighting their unfavorable cardiovascular risk profile, which could potentially have implications not only for themselves but also for their children.<sup>42,43</sup> Maternal smoking during pregnancy is one such early life exposure that may have a persistent influence on offspring body size and cardiovascular health.<sup>21</sup> It is believed that nicotine has a direct effect on the development of the fetal renal, cardiovascular, and nervous systems and an indirect effect through the change in maternal vasculature, affecting placental formation and blood flow.<sup>44</sup> We tested how the different life periods of maternal smoking were associated with children's BP levels and found that exposure to smoking during pregnancy resulted in significantly higher BP levels at the age of 4. We observed that 60% of mothers who reported ever smoking did it in all three periods—before, during pregnancy, and 4 years after—indicating that smoking chronicity might explain the observed results. However, we cannot exclude the possibility of smoking before and/or after pregnancy might also have some effect which could not be documented, given the small number of mothers who reported to smoke only in those periods. Also, although no significant differences were observed, when considering current smoking exposure and dividing mothers into three categories—no, never; no, but before or during pregnancy; and yes—a higher proportion of offspring with high BP levels was observed for mothers who quit smoking, but who had smoked before or during pregnancy (22.0%)

and for those who were currently smoking (21.7%), compared to never smoking mothers (19.3%).

Recent evidence from the Avon Longitudinal Study of Parents and Children has shown that prenatal maternal smoking results in epigenetic changes in the offspring, with persistence of DNA methylation changes into adolescence.<sup>38</sup> Although research in this area is in an early stage, the long-term impact of parental smoking on the offspring epigenome may underlie part of the atherogenic process.<sup>44</sup> Further animal and human studies may help elucidate pathways by which smoking or nicotine exposure before pregnancy might program later BP.

Despite the remarkable progresses in smoking policies,<sup>45</sup> household SHS exposure very much remains a contemporary issue, with the results of the 1999–2008 Global Youth Tobacco surveys of more than 350 000 children revealing that 30.4% were exposed to SHS inside their homes.<sup>44</sup> SHS exposure in children is a human rights issue, namely, because they are unable to choose their own environments and leave smoke-exposed settings. This indicates that involuntary smoking will be a persistent and significant cause of morbidity and mortality in the years ahead.<sup>34</sup>

Policies banning smoking in work and public places have been widely implemented and resulted in CVD reduction.<sup>46</sup> In 2009, the American Academy of Pediatrics called for children to have universal smoke-free home, car, school, and play environments, both inside and outside.<sup>47</sup> Progress continues to be made as bans on smoking in cars with children have been enacted in several countries worldwide.<sup>48</sup>



The acknowledgment that childhood BP tracks into adult life,<sup>16</sup> although the relative contributions of genetic and environmental factors and the effect of reversibility of the latter on long-term BP tracking and adult cardiovascular health are not entirely clarified, reinforces the increasing assurance that avoiding or removing potentially irreversible adverse factors as early as possible are a suitable approach to follow.<sup>13</sup>

## Strengths and Limitations

Since this study is based on a population-based birth cohort, there were losses to follow-up as expected. However, few differences were found between participants included and nonincluded in the present study, which should not have had impact on our results. The assessment of smoking by questionnaire without a biochemical validation and social desirability, leading to underreport of smoking, might be limitations of our study. However, it was shown that self-reporting is a reliable approach to exposure ascertainment,<sup>49,50</sup> and we believe that any underreporting is nondifferential. The population-based life course approach, the BP measurement in preschool age, the evaluation of a comprehensive large group of potential confounders, and the novelty of assessing three different time periods in a prospective cohort design are strengths of the study.

## Conclusion

Using data from a birth cohort with detailed information on maternal smoking as well as BP measurement as early as 4 years of age, we found that maternal smoking before, during, and after pregnancy was independently associated with SBP z-score levels in preschool children. This study provides further reason to support innovative programs to reduce smoking in reproductive-age women.

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## Declaration of Interests

None declared.

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